wording of those claims consistent with the language of claim 1 as amended.

Turning now to the issues raised in the outstanding Official Action, the Action first makes final the restriction requirement initially imposed in the Official Action of January 20, 2000. Notwithstanding the finality of that requirement, if the present amendment is deemed to place independent claim 1 in condition for allowance, then the non-elected dependent claims 15-19 are believed to be ripe for rejoinder therewith, as those claims specify the DNA encoding the fusionprotein of claim 1. Therefore, a recognition of the patentability of claim 1 will at the same time establish that claims 15-19 share a requisite "special technical feature" therewith, pursuant to PCT Rule 13.2. Applicants accordingly respectfully request such rejoinder at this stage.

Turning now to the substantive issues raised in the outstanding Official Action, it is believed that the indefiniteness rejection applied at item 5 of the Official Action is overcome by the present amendment.

In particular, in claims 3, 7, 10-12 and 14, the use of the language "preferably" has been deleted, in response to the Examiner's well-taken formal criticisms.

Similarly, in claim 8 and 11 the term "essential part thereof" is no longer used, although it is believed to be reasonably clear in context that this term simply meant a portion of the recited material having the requisite properties.

Lastly, the term "immunoglobulin properties" in the claims has been preserved, as this term is given reasonably precise definition in the specification, for example at page 5, line 26 through page 6, line 7. Therefore, the recited parts conferring immunoglobulin properties will confer at least those properties allowing the fusionprotein to be coupled to a solid support to be used for purifying plasma from a recipient of a xenotransplant from antibodies against the transplant (page 5, lines 28-31).

It is accordingly believed that the indefiniteness rejection of claims 3 and 7-14 as previously in the case, should not be repeated with respect to any of the claims as amended herewith.

At item 7 of the Official Action, claims 1-4, 9-11 and 13 as previously in the case were rejected as allegedly being unpatentable based on the combined teachings of TSUJI et al., "Specificity of Human Natural Antibody to Recombinant Tissue-Type Plasminogen Activator (t-PA) Expressed in Mouse C127 Cells", *Chem. Pharm. Bull.* **38**(3), March 1990, pp. 765-768 and LINSLEY et al. U.S. Patent No. 5,434,131. That rejection is respectfully traversed, for the following reasons.

TSUJI et al. relate to a recombinant protein expressing the Galα1,3Gal epitope, wherein endogenous DNA is used.

In contrast, the fusionprotein according to the invention has been designed to overexpress the enzyme. As is clear to the skilled in this field from the amended claim 1,

the mucin portion, the amino acid of which comprises 53 potential glycosylation sites, will confer an activity which is superior to the activity of the protein described by TSUJI et al.

Thus, TSUJI et al. show the presence of an antibody binding to Galα1,3Gal in patients. Even though the techniques for producing fusionproteins as such is well known TSUJI et al. neither teach nor suggest coupling a Galα1,3Gal epitope carrying portion to a mucin portion in the form of a fusion-protein. This is hardly surprising, since TSUJI et al. have no intention to use their protein for removing large amounts of antibodies in xenotransplantation. In fact, TSUJI et al. mention nothing about the role of Galα1,3Gal epitope in species associated immunological reactions, such as xenotransplantation, and accordingly give no indication to the skilled even to attempt to design the invention as defined by claim 1.

The greatly enhanced activity of the present fusionprotein is about 100:1, as compared to the recombinant protein of TSUJI et al. Even <u>if</u> the skilled in this field would be inclined to increase the number of glycosylation sites by making a novel protein, after reading TSUJI et al., he would presumably choose to do so by including a greater number of epitopes. However, the present inventors surprisingly found that the enhanced activity is <u>not</u> proportional to the number of epitopes, but should rather be ascribed to the structure in space of the mucin protein.

Evidence of this point appears in the recently-published abstract attached to this letter.

Considering the amended claim 1, the combination of TSUJI et al. with LINSLEY et al. likewise does not suggest the invention. The surprising and inventive feature of claim 1 is the fact that the mucin portion and the multiple Galα1,3Gal epitopes together provide a product which shows a surprisingly high activity. In this context, it is also important to note that the present invention is in fact a product of a combination of two separate technical fields: protein chemistry and carbohydrate chemistry, which is the result of an inventor who changed from one field to the other. This inventor's personal experience from carbohydrate chemistry gave him the idea of using the mucin portion in this context, while however those skilled in the field of protein expression and fusionproteins would normally not have sufficient knowledge about carbohydrates. Thus, even though the skilled artisan in this field may have been motivated to include the IgFc tag as suggested by the Examiner, it required an extraordinary inventive skill to come up with a fusion protein comprising a mucine portion.

At item 8 of the Official Action, claims 1-11 were further rejected based on the same combination of references, and further in view of SAKO et al., "Expression Cloning of a Functional Glycoprotein Ligand for P-Selectin", *Cell*, Vol. 75, December 17, 1993, pages 1179-1186.

The present invention clearly relates to an antigenic fusionprotein, in other words, to antibody mediated reactions.

SAKO et al. on the other hand relate to interactions between circulating leukocytes and endothelium, that is, to cellularly mediated reactions.

Firstly, it is not at all apparent why a skilled person aware of TSUJI et al., in order to solve a problem not even suggested therein, would turn to a document relating to cellularly mediated reactions, in order to combine such totally different mechanisms. Even if he would, he would not come up with the present invention, which is not restricted to, only illustrated by, P-selectin. The invention encompasses any mucin, as was clear from the previous broad wording as well as the amended claim 1.

Secondly, the Official Action then combines TSUJI et al., SAKO et al. and LINSLEY et al. The consideration of two different documents from one field with one document from another field would unlikely be made in the first instance. Even if a person skilled in one of these fields were faced with all three documents, he would not end up with the present invention: there is no pointer in any one of the documents, especially of TSUJI et al. and SAKO et al., to use either one of the Galα1,3Gal epitope or P-selectin as one portion of a fusionprotein, which is explained by the fact that none of the documents suggests the purpose of the invention: to eliminate large amounts of antibodies. Thus, TSUJI et al. express no need to produce a more efficiently binding protein and SAKO et

al. give no indication whatsoever that P-selectin would be useful in the context of antigen-antibody interactions. Even though the mucins are well known to be highly glycosylated, as the Examiner states, that gives no motivation to consider a combination of documents such as the cited references.

At items 9 and 10 of the Official Action, the dependent claims 12 and 14 were rejected based on the same combinations of references applied at items 7 and 8, respectively, each further in view of GODING, *Monoclonal Antibodies: Principles and Practice*, Table 4.2, Academic Press, New York, 1983. While GODING may teach the particular feature for which it was relied upon, in light of the above discussions it is apparent that the further citation does not bring the more basic combinations of references closer to the invention as claimed. Claims 12 and 14 are accordingly believed to be allowable at least by virtue of their dependency from an allowable claim 1.

Lastly, at item 11 of the Official Action, claim 20 was rejected as allegedly being unpatentable based on the same combination of references applied at item 7, further in view of KOZLOWSKI et al., "Apheresis and Column Absorption for Specific Removal of Gal-α-1,3 Gal Natural Antibodies in a Pig-to-Baboon Model", *Transplantation Proceedings*, 29, 961 (1997).

KOZLOWSKI et al. merely teach the desirability of achieving a method such as that claimed. However, as discussed in more detail above in connection with the rejection applied at item 7, neither KOZLOWSKI et al. nor the other

applied references, whether considered singly or in combination, teach or suggest the material necessary to achieve that result, neither do they detract from the surprising nature of the results achieved with the present invention, as evidenced by the present specification and the more recently-generated literature abstract attached.

In view of the present amendment and the foregoing remarks, therefore, it is believed that this application is now in condition for allowance, with claims 1-6, 8 and 10-20, as amended. Allowance and passage to issue on that basis are accordingly respectfully requested.

Respectfully submitted,

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